



***Mindstreams*[™] Cognitive Health Assessment**

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TABLE OF CONTENTS

INTRODUCTION	1
I. THE SYSTEM.....	2
II. COMPUTERIZED COGNITIVE TESTS.....	2
SUBTESTS	2
<i>Verbal Memory</i>	2
<i>Non-Verbal Memory</i>	3
<i>Go-NoGo Response Inhibition</i>	4
<i>Stroop Interference</i>	5
<i>Problem Solving</i>	6
<i>Visual Spatial Imagery</i>	7
<i>Verbal Rhyming</i>	8
<i>Verbal Naming</i>	8
<i>Staged Information Processing Speed</i>	9
<i>Finger Tapping</i>	10
<i>'Catch' Game</i>	10
CORRESPONDENCE WITH TRADITIONAL NEUROPSYCHOLOGICAL TESTS	12
SCORING AND PROCESSING OF MINDSTREAMS DATA	13
MISSING DATA	16
QUALITY CONTROL OF MINDSTREAMS DATA	16
<i>Automatic Quality Control</i>	16
<i>Quality Control of the Human Interface</i>	17
IV. USABILITY	17
GENERAL USABILITY FEATURES.....	17
USABILITY IN THE ELDERLY.....	19
<i>Ease of Use in the Elderly</i>	19
<i>Minimal Confounds in the Elderly</i>	19
REFERENCES	21

INTRODUCTION

Mindstreams computerized tests assess performance across an array of cognitive domains including: memory, executive function, visual spatial perception, verbal function, attention, information processing speed, and motor skills. The psychometric properties of the tests exploit the advantages of computerized testing, providing precise accuracy and reaction time measurements. *Mindstreams* offers an unbiased, standardized, accurate and inexpensive tool with a wide range of applicability in clinical medicine.

Mindstreams tests demonstrate good construct validity in that there is considerable correspondence between traditional neuropsychological tests and *Mindstreams* tests that tap similar cognitive domains (see Section II below). Discriminant validity in detecting mild Alzheimer's disease has also been shown for *Mindstreams* tests (Dwolatzky, Whitehead et al., submitted). Alternate forms of *Mindstreams* tests were developed for purposes of repeat testing to minimize learning and have indeed shown minimal learning and good test-retest reliability across testing sessions (Schweiger, Doniger et al., submitted).

This document serves as a guide to the design of the *Mindstreams* cognitive tests and the accompanying computerized system. Section I gives a broad overview of the system. Section II provides a theoretical framework and detailed description for each of the tests. The cognitive domains assessed by each of the tests are indicated, and data on correspondence between the *Mindstreams* tests and traditional neuropsychological tests is provided. Section III describes the steps involved in processing the test data by the *Mindstreams* system. Procedures for handling missing data and quality control of the data are addressed. Finally, Section IV concentrates upon usability of the *Mindstreams* tests and system. The section begins with a discussion of general usability features and concludes with features relevant to the elderly, a population for which *Mindstreams* was specifically designed.

I. THE SYSTEM

The NeuroTrax assessment system is built for optimal convenience and ease of use. Further, it incorporates all the security and privacy features required by the FDA.

Registered users of *Mindstreams* may download the Windows-based testing software to their local machine and access the NeuroTrax system via www.mindstreamshealth.com for clinical use or via www.neurotrax.com for research use. Users may enroll participants¹ and order testing sessions via the appropriate website.

Ordered testing sessions are downloaded from the website to the user's local machine where the *Mindstreams* testing software is installed. The user then runs the ordered testing sessions locally and uploads the results to the NeuroTrax server via the Internet.

II. COMPUTERIZED COGNITIVE TESTS

Subtests²

Verbal Memory

Cognitive Domains: immediate recognition memory, delayed recognition memory

➤ Theoretical Framework

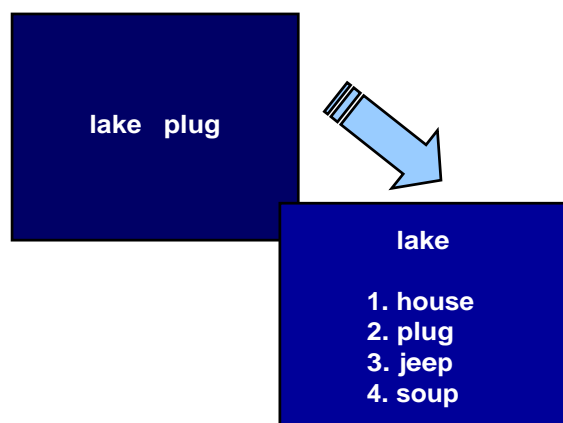
The formation of new associations between items is critical for establishing episodic memories. Yet elderly individuals who suffer from cognitive decline have trouble forming these new associations (e.g., Fowler, Saling et al., 2002). The *Mindstreams* verbal memory test, inspired by the Logical Memory test of the Wechsler Memory Scale, 3rd Edition (WMS-III), is designed to detect such impairment. Strength of association is varied among word pairs presented at study and foils presented at test to yield the appropriate range of performance to distinguish among healthy elderly and those with cognitive impairment (see Nelson, Zhang et al. 2001).

➤ Test Description

The Verbal Memory test measures immediate and delayed recognition memory for verbal paired associates. Participants are presented with 10 pairs of words to study followed by a recognition test in which they are presented with one member of a previously presented pair together with four possible alternatives for the other member of the pair. Responses are made using the keyboard number pad to indicate which

¹ For purposes of this document, 'participant' refers to any individual tested with the NeuroTrax system, irrespective of whether the testing is for clinical or research purposes.

² Screenshots are adaptations of screens presented during actual testing and are provided for illustration purposes only.



pair was previously presented. Four consecutive study/test repetitions follow immediately, and an additional recognition test is administered following two other *Mindstreams* tests for delay period of approximately 10 minutes. Outcome parameters³ include accuracy four each of the four immediate recognition tests, total accuracy across these repetitions, and accuracy for the delayed recognition test. Slope of learning across repetitions is also computed.

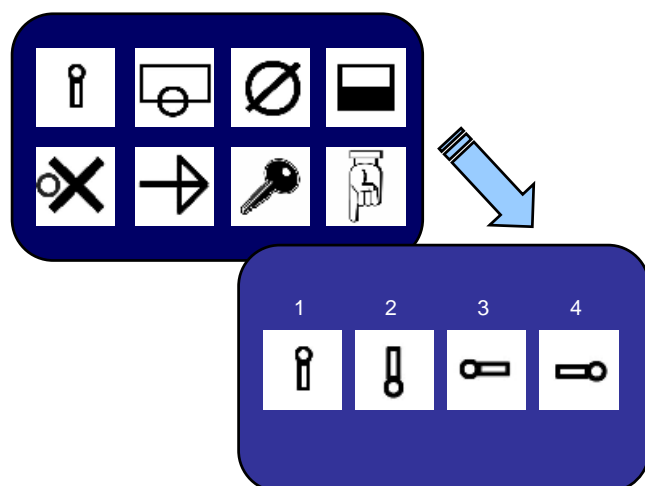
Non-Verbal Memory

Cognitive Domains: immediate recognition memory, delayed recognition memory

➤ Theoretical Framework

Non-verbal memory performance has been shown to be a better predictor of early Alzheimer's disease than even performance on verbal tests (Kawas, Corrada et al., 2003). Like the paper-and pencil Benton Visual Retention Test (BVRT) and Brief Visuospatial Memory Test (BVMt), the *Mindstreams* Non-Verbal Memory test assesses memory for the spatial orientation of geometric visual designs. The repeated study-recognition test format is used to facilitate better comparison across Verbal and Non-Verbal memory tests.

➤ Test Description



The Non-Verbal Memory test measures immediate and delayed recognition memory for the orientation of simple geometric patterns and symbols. Participants are presented with an array of eight simple geometric patterns and are required to remember their orientation. Immediately following is a recognition test in which four possible alternatives are presented, each depicting one of the previously presented patterns facing a different direction. Participants use the keyboard number pad to indicate which

of the four alternatives exactly matches a previously presented pattern. As with the Verbal Memory test, four consecutive study/test repetitions follow immediately, and an

³ See Section III below for details on the computation of outcome parameters.

additional recognition test is administered following a delay of approximately 10 minutes with two other *Mindstreams* tests intervening. Outcome parameters include accuracy for each of the four immediate recognition tests and for the delayed recognition test. Slope of learning across repetitions is also computed.

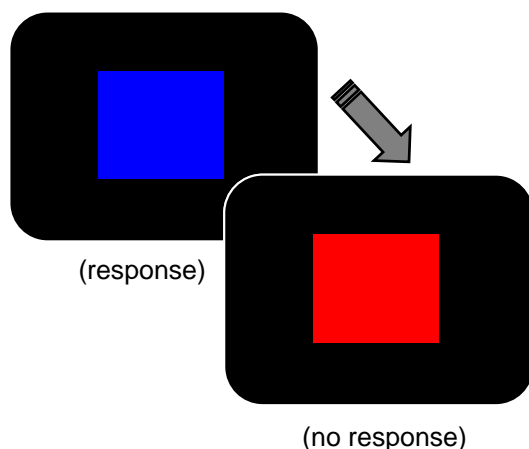
Go-NoGo Response Inhibition

Cognitive Domains: attention, executive function

➤ Theoretical Framework

The *Mindstreams* Go-NoGo test is a variant of the Continuous Performance Task (CPT), which has been shown in hundreds of studies to index attention and executive function (Riccio and Reynolds, 2001). In the most common variant of the CPT, a string of English letters is presented sequentially and responses are made immediately following the presentation of any letter but X. For added robustness, the *Mindstreams* Go-NoGo test utilizes large colored squares similar to the TOVA (Greenberg and Waldman, 1993). Omission errors are thought to reflect deficient sustained attention or vigilance; commission errors are thought to reflect a combination of underlying processes, including impulsivity and inattention/memory deficit (Halperin, Wolf et al., 1991). CPTs have been shown to discriminate multiple clinical groups from healthy individuals, including adults with head injuries (e.g., Burg, Burright et al., 1995) and children and adults with attention-deficit-hyperactivity disorder (e.g., Holmes, Hever et al., 2002; Ossmann and Mulligan, 2003).

➤ Test Description



The Go-NoGo test is a test of simple reaction time and response inhibition. Participants are presented with a series of large colored squares at variable delays. Each square may be one of four colors. Participants are instructed to respond as quickly as possible by pressing a mouse button if the square is any color but red. Outcome parameters include accuracy, reaction time and its associated variance, a composite score computed as accuracy divided by reaction time, number of errors of omission, number of errors of commission, and reaction time associated with errors of commission.

Stroop Interference

Cognitive Domains: attention, executive function

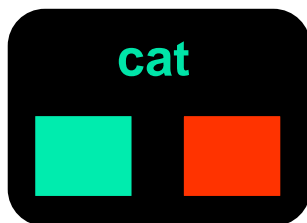
➤ Theoretical Framework

The Stroop is a well-established cognitive test (MacLeod, 1991) that measures the facility with which an individual can shift his perceptual set to conform to changing demands and suppress a habitual response in favor of an unusual one (Spreeen and Strauss, 1998). As with the CPT, there are numerous versions of the Stroop Test, dating back to the original developed by Stroop himself in 1935. The key comparison is between a condition in which responses are habitual (e.g., indicate the color of the letters) and a condition in which responses are unusual (i.e., indicate the color of the letters despite the fact that they spell a different color-word). The Stroop test has been shown to discriminate among brain-damaged individuals, those with schizophrenia, Parkinson's disease, and Huntington's disease (e.g., Batchelor, Harvery et al., 1995; Hanes, Andrewes et al., 1996). Perrett (1974) and Stuss et al. (2001) have reported that the Stroop interference effect is greater for patients with frontal lobe damage than for other groups, supporting the notion that the Stroop interference effect indexes executive function. Importantly, the Stroop test has also been shown to index severity of dementia (Koss, Weiner et al., 1984).

➤ Test Description

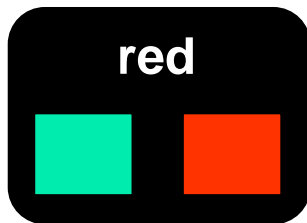
Like the Go-NoGo test, the Stroop test measures simple reaction time and response inhibition. The *Mindstreams* Stroop test consists of three phases. Outcome parameters for each phase include accuracy, reaction time and its associated variance, and a composite score computed as accuracy divided by reaction time.

Phase I



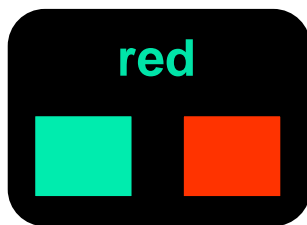
In Phase I, participants are presented with a word in colored letters, with the stipulation that the word does not name a color. Following a brief delay, participants are presented with a pair of colored squares, one on the left and the other on the right. They are instructed to choose as quickly as possible which of the two squares is the same color as the letters of the word presented immediately prior (e.g., blue) by pressing either the left or right mouse button, depending upon which of the two squares is the correct color.

Phase II



For Phase II, participants are presented with a word that names a color in non-colored letters. As in Phase I, participants are then presented with a pair of colored squares and must choose as quickly as possible which square is the color named by the color word presented immediately prior.

Phase III



In Phase III, participants are presented with a word that names a color in letters of a color other than that named by the word. As in Phase I, participants must choose as quickly as possible which of two squares is the same color as the letters of the word presented immediately prior. The conflicting information provided by the meaning of the word and the color of its letters lead to a decrement in performance relative to the other phases

where there is no conflict. This reduced performance is termed the “Stroop” interference effect and is a classical finding in cognitive psychology.

Problem Solving

Cognitive Domains: executive function, abstract reasoning

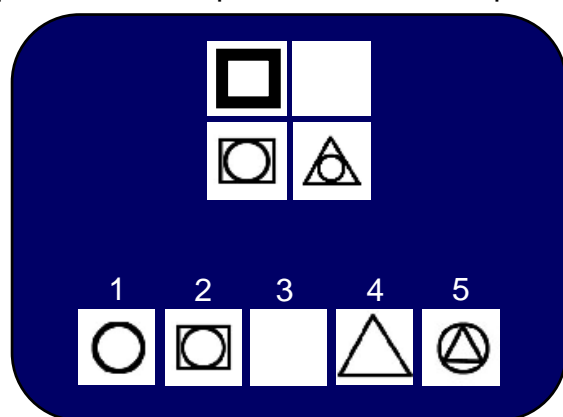
➤ Theoretical Framework

The *Mindstreams* Problem Solving test assesses the ability to appreciate the spatial relationships among geometric forms that constitute a pattern. The test is modeled upon the Test of Nonverbal Intelligence, 3rd Edition (TONI-3; Pro-Ed, Austin, TX, 1997), which measures general intelligence, aptitude, and abstract reasoning. As the TONI and other similar paper-based tests (e.g., Raven's Colored Progressive Matrices, Quick Test of Intelligence), the *Mindstreams* Problem Solving test is language-free and therefore permits assessment of individuals with disorders of communication (e.g., aphasia, dyslexia, autism, cerebral palsy). Ethnic bias is also reduced in this test as the abstract geometric forms are devoid of cultural significance.

➤ Test Description

Participants are presented with an incomplete pattern consisting of three squares containing simple geometric forms in a particular configuration. Six additional squares containing geometric forms are presented along the bottom of the screen. Responses with the keyboard number pad indicate which of the six forms best completes the pattern. The spatial relationships among the simple geometric forms become more complex as the test progresses, and the test is adaptive in that it terminates early when

performance is poor. The outcome parameter for this test consists of a total accuracy score that incorporates performance at differing levels of difficulty.



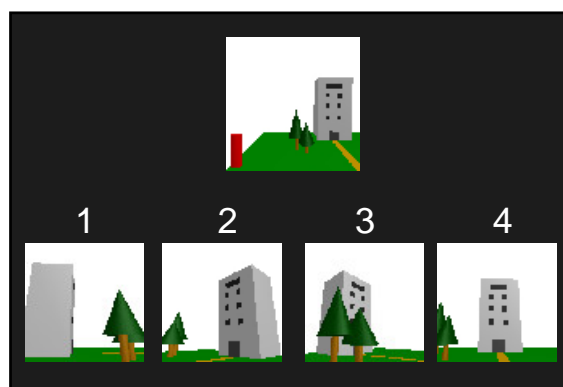
Visual Spatial Imagery

Cognitive Domain: visual spatial perception

➤ Theoretical Framework

Individuals with Alzheimer's disease get lost in familiar surroundings, in part, because of visuospatial disorientation. Indeed there is ample evidence that individuals with Alzheimer's disease are impaired in visual-spatial perception (Butter, Trobe et al., 1996; Rizzo, Anderson et al., 2000). Hence included in the *Mindstreams* mild impairment battery is a novel test of visual-spatial perception designed to assess ability to perceive such features as depth, shape, and size, each of which may operate independently to permit accurate visual-spatial perception in the real world (see Brenner and van Damme, 1999).

➤ Test Description



The Visual Spatial Imagery test assesses abstract spatial ability. Participants are presented with a computer-generated everyday scene containing a red *pillar* (rectangle). They are instructed to imagine standing at the location of the red pillar. Four views of the scene are presented at the bottom of the screen, and participants are required to indicate using the keyboard number pad which of the four views corresponds to the view of the scene from the location of the *pillar*.

Verbal Rhyming

Cognitive Domains: language skills, semantic knowledge

➤ Theoretical Framework

Impairment in verbal fluency is a telltale sign of dementia, especially in its more advanced stages (e.g., Monsch, Bondi et al. 1992). Paper-based verbal fluency tests typically require the naming of common objects within a semantic category or those that begin with a particular letter (e.g., Kitabayashi, Ueda et al., 2001). *Mindstreams* language tests are designed to assess this cognitive domain but are adapted for computer-based administration. The Verbal Rhyming test is a novel test that taxes not only naming ability, but also the higher-order ability to form an association among similar-sounding words. Indeed there is some evidence for a deficit in phonological processing in Alzheimer's disease (Biassou, Grossman et al., 1995) and hence this test is included as part of the mild impairment battery.

➤ Test Description



The Verbal Rhyming test assesses higher-order verbal skill. Participants are presented with a picture of a common object of either low or high familiarity. Following a brief delay, a list of four words appears on the screen. Participants are instructed to respond as quickly as possible by using the keyboard number pad to indicate which one of the four words rhymes with the name of the preceding picture. Outcome parameters include accuracy for low and high familiarity objects and an overall accuracy score.

Verbal Naming

Cognitive Domains: language skills, semantic knowledge

➤ Theoretical Framework

The *Mindstreams* Verbal Naming test assesses ability to name low-familiarity pictures, a skill shown to be selectively impaired in Alzheimer's disease and due to some combination of perceptual and semantic dysfunction (Goldstein, Green et al., 1992, Auchterlonie, Phillips et al., 2002). In addition to assessing naming deficit in dementia, Naming test performance serves as a control for the Rhyming test. The same items are presented in both tests, and performance on the Rhyming test is excluded for any items that are not namable on the Naming test. This design is based on the premise that ability to name is a prerequisite for ability to rhyme. Hence *Mindstreams* language tests offer sensitivity to multiple stages of verbal fluency impairment.



➤ Test Description

The Verbal Naming test assesses basic verbal skill. Participants are presented with the same low familiarity pictures of common objects as on the Verbal Rhyming test. As in the Rhyming test, a list of four words appears following a brief delay. Now participants must respond by indicating which of the four words presented names the preceding picture. The outcome parameter for this test is accuracy.

Staged Information Processing Speed

Cognitive Domains: attention, arithmetic ability, information processing speed

➤ Theoretical Framework

Arithmetic ability has been shown to correlate more highly with other neuropsychological predictors of Alzheimer's disease than even the standard MMSE (Rosselli, Ardilla et al., 1998). Further, mathematical ability has been identified as a good predictor of general intellectual function in Alzheimer's disease. The *Mindstreams* test of Staged Information Processing Speed utilizes simple arithmetic, equally taxing across a range of educational levels, to reveal differences in performance as a function of stimulus presentation rate. The test is designed to exploit the advantages of computer-based testing to accurately assess information processing speed. Its multi-level, timed format is fashioned to incrementally tax cognitive resources, providing a precise indicator of extent of impairment.

➤ Test Description



The Staged Information Processing Speed test measures information processing at increasing levels of complexity. The test is comprised of three levels of information processing load: single digits, two-digit arithmetic problems (e.g., 5-1), and three-digit arithmetic problems (e.g., 3+2-1). For each of these three levels, stimuli are presented at three different rates, incrementally increasing as testing continues. Participants are presented with a series of digits or arithmetic problems (as per the level) and are

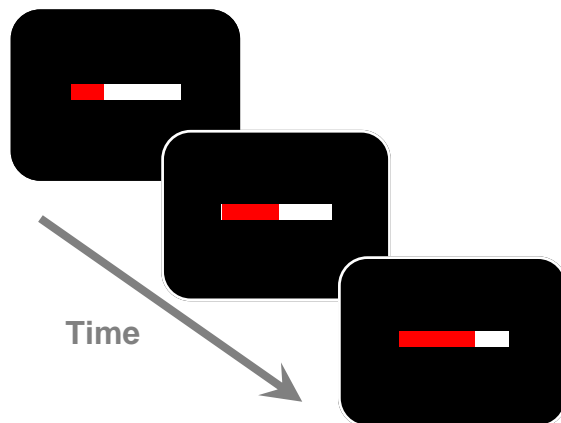
instructed to respond as quickly as possible by pressing the left mouse button if the digit or result is less than or equal to 4 and the right mouse button if it is greater than 4. Outcome parameters for each rate increment for each level include accuracy, reaction time and its associated variance, and a composite score computed as accuracy divided by reaction time.

Finger Tapping

Cognitive Domain: motor speed

➤ Theoretical Framework

Though not as prominent as cognitive decline, motor dysfunction occurs in Alzheimer's disease, particularly in the later stages of the disease. Kluger et al. (1997) have shown that tests of motor skill can distinguish between even mildly impaired and normal individuals. These authors found that motor/psychomotor assessments are equally sensitive to traditional tests of cognitive function in identifying early AD. Tests of finger tapping have been utilized in clinical contexts from stroke to Parkinson's disease to Attention-deficit-hyperactivity-disorder (ADHD) to index fine motor skills (Pal, Lee et al., 2001; Zemke, Heagerty et al., 2003; Pitcher, Piek et al., 2002). The novel *Mindstreams* Finger Tapping test is designed to quantify fine motor function in individuals with mild cognitive impairment.



➤ Test Description

Participants are presented with a white rectangle, which fills with red from left to right over 12 sec. The task requires the participant to tap the left mouse button as many times as possible while the rectangle fills with red. The outcome parameters for this test include inter-tap interval and associated variance (in milliseconds) for the participant's dominant hand.

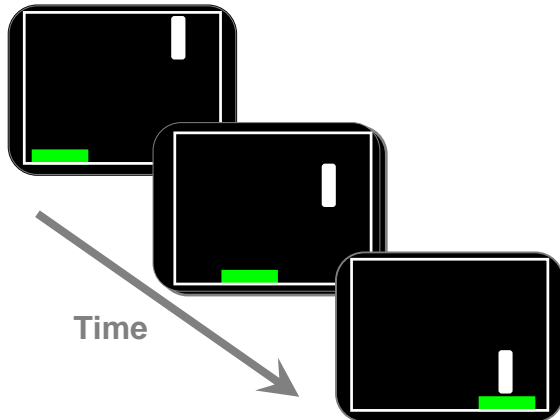
'Catch' Game

Cognitive Domains: attention, executive function, visuomotor planning

➤ Theoretical Framework

The 'Catch' Game is a novel motor screen that assesses cognitive domains distinct from those in other *Mindstreams* tests, including motor-related reaction time, motor learning, motor planning, and performance speed. Importantly, individuals with Alzheimer's disease have shown impairment on a response programming task measuring preparation and execution of movements (Bellgrove, Phillips et al., 1997). The 'Catch' Game assesses similar skills with an engaging video-game format that utilizes adaptive testing and capitalizes upon the fine timing possible with a computerized system.

➤ Test Description



During the 'Catch' Game participants see a rectangular white *object* falling vertically from the top of the screen. Their task is to “catch” the *object* before it reaches the bottom of the screen by positioning the rectangular green *paddle* directly in the path of the falling object. The *paddle* is a green rectangle that can be moved horizontally across the bottom of the screen. Participants position the *paddle* by pressing the left mouse button to move the *paddle* leftward and the right button to move it rightward. Responses are made with the

participant's best hand. The rate of the falling *object* increases incrementally as the test continues making it increasingly difficult to “catch” the object in time. Outcome parameters include reaction time and associated variance for the first move, number of direction changes per trial, error for missed catches, total number of trials completed, and a total performance score.

Correspondence with Traditional Neuropsychological Tests

Table 1. Comparison of *Mindstreams* computerized tests with traditional paper-based neuropsychological tests in healthy elderly, ($N=15$), those with mild cognitive impairment ($N=20$), and those with dementia ($N=19$).

<i>Mindstreams</i> Test (outcome parameter)	Traditional Paper-Based Measures	Correlation <i>r</i> -value ^{AB}
Verbal Memory (accuracy: final repetition, immediate recognition test)	WMS-III Logical Memory II	0.73
	WMS-III Logical Memory I	0.70
	WMS-III Visual Reproduction II	0.70
Non-Verbal Memory (accuracy: final repetition, immediate recognition test)	RAVLT Short Term Retention	0.77
	WMS-III Visual Reproduction II	0.72
	WAIS-III Digit Symbol	0.71
	RAVLT Delayed Recall	0.70
	WMS-III Logical Memory I	0.70
	WMS-III Logical Memory II	0.70
	WMS-III Visual Reproduction I	0.68
	RAVLT Total Learning	0.61
Go-NoGo (composite score)	Stroop Word Time	-0.81
	Stroop Color Word Time	-0.71
	Controlled Oral Word Association A	0.69
	WAIS-III Digit Symbol	0.68
Stroop Phase III (composite score)	Stroop Color Word Time	-0.52
	Controlled Oral Word Association A	0.50
	WAIS-III Letter-Number Sequencing	0.47
Visual Spatial Imagery (accuracy)	WAIS-III Digit Symbol	0.60
	WMS-III Mental Control	0.57
	WAIS-III Spatial Span	0.57
Verbal Rhyming (weighted accuracy)	Controlled Oral Word Association A	0.64
	Boston Naming Test	0.62
	WMS-III Logical memory I	0.62
	Controlled Oral Word Association FS	0.61
Staged Information Processing (overall composite score)	WMS-III Mental Control	0.76
Problem Solving (accuracy)	WAIS-III Block Design	0.66
	WAIS-III Similarities	0.61
'Catch' Game (weighted accuracy)	WAIS-III Block design	0.60
	WAIS-III Digit Symbol	0.51

^A $p < 0.05$ for all reported correlations

^B Pearson correlations shown only when *r*-value was greater than for correlation with MMSE.

RT: reaction time NS: not significant

(adapted from Dwolatzky et al., submitted)

III. Data Processing

Scoring and Processing of *Mindstreams* Data

The following scheme applies to *Mindstreams* tests with accuracy, reaction time and composite score outcome parameters.

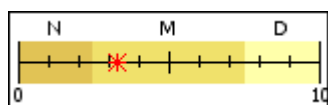
1. *Mindstreams* generates **raw data** consisting of information related to each individual trial including: stimulus type, onset and offset of the stimulus (in milliseconds), expected response type, actual response type, and time of response.
2. When data is uploaded to the NeuroTrax central computer, accuracy for each trial is determined by whether expected and actual response types match. Reaction time is calculated as the difference between time of response and stimulus onset.
3. **Accuracy outcome parameters** are calculated as the average accuracy across all trials included in a particular level of a test. Similarly, *reaction time* outcome parameters are calculated as the average accuracy across all trials in a level. *Composite score* outcome parameters are computed as average accuracy divided by average reaction time for a level, which adjusts for the speed-accuracy tradeoff (e.g., Osman, Lou et al., 2000). *Standard deviation of reaction time* outcome parameters are computed as the standard deviation (i.e., a measure of variance) of the reaction times across all trials in a level. Other test-specific outcome parameters (e.g., inter-tap interval for the Finger Tapping test) are generated in a similar manner, as appropriate for the test.
4. Once computed, outcome parameters are normalized according to age- and education-specific normative data.⁴ Groups of normalized parameters that tap similar cognitive functions are then averaged to produce a single **index score** reflecting performance in a particular cognitive domain. Index scores currently computed by *Mindstreams* and the outcome parameters they comprise are listed in Table 2.

⁴ Normative data are generated from healthy individuals in controlled clinical trials.

Table 2. *Mindstreams* index scores and their constituent outcome parameters.

Index Score	<i>Mindstreams</i> Test outcome parameter(s)
Memory	Verbal Memory mean accuracy across repetitions, immediate recognition test accuracy, delayed recognition test Non-Verbal Memory mean accuracy across repetitions, immediate recognition test accuracy, delayed recognition test
Executive Function	Go-NoGo composite score Stroop, Phase III composite score 'Catch' Game weighted accuracy
Visual Spatial Perception	Visual Spatial Imagery accuracy
Verbal Function	Verbal Rhyming weighted accuracy
Attention	Go-NoGo reaction time standard deviation of reaction time Stroop, Phase II reaction time Staged Information Processing Speed accuracy, two-digit arithmetic (fast presentation rate) reaction time, single digit (medium presentation rate)
Information Processing Speed	Staged Information Processing Speed reaction time difference between: two-digit arithmetic & single digit (slow presentation rate) two-digit arithmetic & single digit (medium presentation rate) three-digit arithmetic & two-digit arithmetic (medium presentation rate)
Motor Skills	Staged Information Processing Speed inter-tap interval standard deviation of inter-tap interval 'Catch' Game reaction time for first move

5. The **Global Cognitive Function (GCF)** score is computed as the average of the seven index scores. Together with its constituent index scores, the GCF score appears on the clinical assessment reports produced by the *Mindstreams* system.
6. For purposes of discriminating among healthy elderly and those with cognitive



N = 100% healthy elderly zone
M = middle zone
D = 100% AD zone

* = score of sample participant (3.3)

impairment, the system computes an **MCI Score**. This score is built from six outcome parameters that span a range of cognitive domains and show good sensitivity and specificity for discriminating individuals with mild Alzheimer's disease from healthy elderly (Table 3). For each of these outcome parameters, cutoffs for the best balance between sensitivity and specificity

were identified based upon a cohort of patients drawn from the registry of a well-established tertiary care referral center for evaluation of memory complaints.

Performance on each outcome parameter is scored as either pass (0) or fail (1), depending upon whether it is above or below the cutoff, respectively. The total number of failures on the six outcome parameters is scaled to a 10-point scale to yield the MCI Score. Based upon our reference sample, the 10-point scale is subdivided into a zone 100% specific for healthy elderly (0 to 2.5; no individuals with AD appeared in this zone), a zone 100% specific for AD (7.5 to 10; no healthy elderly appeared in this zone), and a middle zone (2.5 to 7.5 both healthy elderly and those with AD appeared in this zone).

Table 3. Discriminant validity of *Mindstreams* MCI Score and its constituent outcome parameters: optimal sensitivity/specificity, associated cutoff, and a measure of effect size (Cohen's *d*); validity of paper-based MMSE and ADAS-cog shown for comparison

<i>Mindstreams</i> Test (outcome parameter)	Sensitivity	Specificity	Cutoff	Cohen's <i>d</i>
Verbal Memory (accuracy: final repetition, immediate recognition test)	1.0	0.95	85	4.32
Non-Verbal Memory (accuracy: final repetition, immediate recognition test)	0.96	0.89	56	3.12
Go-NoGo (composite score)	0.80	0.86	0.18	1.77
Stroop Phase III (composite score)	0.83	0.84	0.053	1.63
Visual Spatial Imagery (accuracy)	0.76	0.78	47	1.57
Catch Game (mean weighted accuracy)	0.83	0.84	429.5	1.58
<i>Mindstreams</i> MCI Score	0.96	0.90	3.5	3.97
MMSE	0.86	0.97	27.5	2.00
ADAS-cog	0.93	0.92	13.8	2.42

(adapted from Dwolatzky et al., submitted)

Missing Data

1. For a given test, missing raw data may result from early termination of the test, lack of responses by the participant, or failure of the practice session.
 - a. If there is missing data due to early termination of the test or lack of responses, *Mindstreams* determines whether there is sufficient data for each test level to warrant inclusion of that data in subsequent computations. If not, data for the entire level is treated as missing.
 - b. If test data is missing due to failure of the practice session, *Mindstreams* inserts a value for each outcome parameter equivalent to 2.5 standard deviations below the mean score for an age- and education-matched normative sample.
 - i. *Mindstreams* replaces performance on a given outcome parameter poorer than 2 standard deviations (SDs) below the mean score for age- and education-specific normative data with the value equivalent to 2 SDs below the normative mean. This correction ensures that individuals who fail the practice session will receive a poorer score than those who perform poorly on the actual test.
 - ii. *Mindstreams* ensures that values inserted due to failure of the practice session or poor performance on the actual test can never result in a negative accuracy score by truncating all such scores at 0.

Quality Control of *Mindstreams* Data

Mindstreams contains automatic quality control features, in addition to quality control of the human interface to ensure the integrity of the cognitive data, as detailed below.

Automatic Quality Control

1. Full data security features, including firewall, triple DES encryption, secure socket layer, audit trails, and password protection.
2. Continuous checks of the local testing computer for adequate performance throughout the testing session, as it relates to the accuracy of timing measurements.
3. Automatic detection of incomplete data (see *Missing Data* above) and data out of expected ranges.
4. Automatic detection of data patterns that might be associated with computer malfunction.
5. Immediate alert of NeuroTrax personnel upon detection of a potential technical error. Processing of affected test data is halted unless cleared by NeuroTrax personnel.
6. Automatic detection of performance patterns that might indicate invalid participant performance. Algorithms are in place to determine whether the participant is:
 - a. devoting adequate effort to completing the test, and

- b. responding according to instructions
- 7. Notification of physician/investigator regarding a suspected invalid result.

Quality Control of the Human Interface

During the testing session, it is critical that the participant be comfortable with the computerized testing environment. Moreover, it is important that the participant be able to carry out the instructions for each *Mindstreams* test. Hence:

1. The first time an individual is tested, a brief orientation to the computer precedes the tests. During this session, he/she is trained to use the mouse and keypad buttons for responses. In addition, visual acuity and color discrimination are tested to the degree necessary for valid completion of the *Mindstreams* tests. The individual will not be given tests critically dependent upon a skill for which he/she was unable to demonstrate proficiency during the orientation session.
2. Each test has a practice session prior to the actual test. During the practice session, the participant is taught the mechanics of the test while the cognitive task remains trivial. If the participant fails (i.e., scores below a certain threshold accuracy) two practice sessions, he is not given the actual test, and the system advances to the next test in the battery.
3. NeuroTrax recommends that a test supervisor be present to ensure that the participant understands the test instructions and genuinely completes the tests.

IV. USABILITY

General Usability Features

The *Mindstreams* system is designed for ease of use in any target population. The following is a treatment of general usability features:

1. **Test supervisor requires only minimal training.** Because tests are easily understood and automatically processed and scored, *Mindstreams* does not have to be administered by a trained psychologist. Test administrators have been receptionists, research assistants, students, and technicians. A single 2- to 3-hour training session is required for certification as a *Mindstreams* test supervisor.
2. **Brief testing time.** Compared with traditional neuropsychological testing batteries (testing time: ~4-6 hours), *Mindstreams* testing batteries offer assessment of a broad array of cognitive domains within a minimal testing time. Administration time varies with the set of tests that comprise the battery and the level of impairment of the participants. Actual test times for each test subdivided by age appear in Table 4.

Table 4. Test times (in minutes) for *Mindstreams* tests.

<i>Mindstreams</i> test	under 65		65 and over	
	Mean	SD	Mean	SD
Verbal Memory	5.64	2.91	9.49	4.14
Non-Verbal Memory	4.58	2.24	6.72	2.86
Go-NoGo Response Inhibition	2.74	2.52	2.68	0.86
Stroop Interference	4.69	2.60	5.48	1.60
Problem Solving	5.00	1.88	5.55	2.38
Visual Spatial Imagery	4.16	2.20	5.06	1.89
Verbal Rhyming/Naming	7.76	2.51	10.47	4.34
Staged Information Processing	5.71	2.15	5.72	1.78
Finger Tapping	1.72	0.54	2.01	0.97
'Catch' Game	2.96	0.67	2.85	1.05
Total	44.95	20.21	56.03	21.86

3. **Easy set-up and start-up.** The NeuroTrax system was designed to facilitate easy set-up and start-up. No special equipment is required, only a standard personal computer and an Internet connection. Hence testing can be performed wherever such facilities are available.
4. **Immediate graphical assessment reports.** The *Mindstreams* clinical assessment report, which is the formal result of a clinical testing session, is available on-line within seconds of uploading the data. Integral to this report is the standardization of performance according to age- and education-matched normative data. The report further contains a longitudinal timeline comparing performance from prior testing sessions to that of the current session.
5. **Multiple languages.** *Mindstreams* is available in multiple languages. Currently, these include English, Hebrew, Russian, and Spanish.
6. **Repeated Testing.** *Mindstreams* batteries in each language are available in multiple alternate forms, which have shown high reliability with repeat testing (Schweiger, Doniger, Dwolatzky, Jaffe, and Simon, submitted).
7. **Practice sessions.** Prior to each *Mindstreams* test there is a short practice session (see Section III above). The practice sessions, which consist of trials of low difficulty, serve the following purposes:
 - a. Familiarize participant with the mechanics of each test.
 - b. Determine if performance is too low. If the practice session is failed, then a second practice session is given. If both practice sessions are failed, then the actual test is automatically skipped.
 - c. Ensure validity of test data. Satisfactory completion of the practice session is taken as evidence that data from the subsequent test is valid (subject to additional criteria as above).
8. **Lack of Ceiling and Floor Effects.** A major limitation of paper-based testing is the presence of ceiling and floor effects. That is, either the test is too easy or too

difficult for the target population. *Mindstreams* avoids these ubiquitous effects with adaptive testing that gradually increases the level of difficulty or terminates the test depending upon performance on earlier levels. For individuals with severe cognitive impairment (MMSE: ~10 to ~26), NeuroTrax has developed a “dementia battery” containing tests especially designed for performance at a lower level relative to the other batteries which include the main tests described above (Section II).

Usability in the Elderly

The *Mindstreams* user interface has specific design features tailored for ease of use by elderly individuals and to minimize potential confounds in this target population.

Ease of Use in the Elderly

A successful cognitive test must be easy to use. With this in mind, the following considerations were addressed in the design of the *Mindstreams* user interface to facilitate testing in the elderly:

1. **Not frustrating or embarrassing.** Traditional neuropsychological testing performed by a psychologist is confrontational. Participants have the uncomfortable feeling that they are being judged. In contrast, with the computer-based administration of *Mindstreams* tests, this issue is eliminated.
2. **Brief and flexible.** Paper-based neuropsychological testing batteries (test time: ~4-6 hours) must typically be completed regardless of performance. In contrast, *Mindstreams* tests are adaptive, terminating automatically if the participant performs poorly on less difficult levels of each test (see below for test times).

Experience with over 500 elderly participants to date indicates that older individuals can perform *Mindstreams* tests. Indeed healthy elderly, those with mild cognitive impairment (MCI), and even those with mild dementia (MMSE>22) have been able to perform the tests with minimal supervision (see below). Further, test supervisors have repeatedly reported that elderly participants are comfortable with *Mindstreams* because they are not scored or judged by another person.

Minimal Confounds in the Elderly

A successful cognitive test must validly assess cognitive performance and be free of other potentially confounding factors. With this guiding principle, the following potential confounds in testing the elderly were identified and addressed in the design of the *Mindstreams* user interface:

1. **“Intimidation” by computers**, especially by use of the mouse to control a cursor and by typing on the keyboard. Hence, *Mindstreams* tests require neither manipulation of a cursor nor typing on the keyboard. Rather, most tests require only that the participant press mouse buttons. Use of the mouse buttons is

quickly learned during the computer orientation session (see Section III above) that precedes the tests. The remainder of the tests requires that the participant press numbers on the number pad. The number pad is intuitively familiar due to its similarity to the telephone number pad. Indeed a recent study of 97 older individuals, including healthy elderly, those with MCI, and those with mild dementia, demonstrated that prior computer experience did not confound the ability for each test to separate between the groups.⁵

2. **Hearing impairment.** If auditory stimuli were used, there would be a potentially serious confound of degree of hearing impairment and possibly also volume setting on the computer speakers. Hence, *Mindstreams* tests do not rely upon auditory stimuli.
3. **Limited manual dexterity due to arthritis or other difficulties.** Such difficulties constitute confounds for timed tests, in particular, since erratic reaction times and accompanying variance in reaction times may be a direct result of the motor impairment. Hence, we avoided use of a touch screen, where the complexity of the motor response requires stability of the finger in space and recruits a coordination mechanism from shoulder, elbow, wrist, and finger joints. *Mindstreams* requires manual responses of minimal complexity on timed tests. The participant's hand rests on the mouse and with the index and middle fingers used for responses poised over the buttons.
4. **Difficulty seeing fine details in letters and images.** Therefore, *Mindstreams* tests use a large font size (64 point) and large images. Detailed stimuli are avoided so that the salient elements are easily discernible, and potential confound due to visual impairment is reduced. To ensure the efficacy of this approach, part of the computer orientation session (see Section III) preceding the tests is designed to determine whether the participant can satisfactorily discern the critical information in words and figures similar to those presented in the tests themselves.

⁵ The only exception was the 'Catch' Game, for which there was a weak effect of computer experience upon the ability of the tests to discriminate among healthy and impaired individuals (Dwolatzky et al., submitted).

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